Remarks

Restriction/Election: The Applicants affirm the election to prosecute the invention of Group I, Claims 23-52 and 99-105 and the peptide substrate species of SEQ ID NO:11. Consistent with the election, Claims 1-22, 25-28 (withdrawn by Examiner), 53-98 and 106-111, being withdrawn from further consideration, are hereby cancelled.

Amendment of the specification: On pages 2-7 of this paper, the Applicants have requested correction of minor typographical and wording errors in the specification. The amendments contain no new matter.

Amendment and cancellation of claims: On pages 8-13 of this paper, in the listing of Claims, Applicants request amendment of specific claims and cancellation of other claims in response to the Examiner's rejection of the Claims of Group I. The following remarks discuss the amendments with the intent of demonstrating to the Examiner that the Claims remaining in the case, as amended, are now in condition for allowance.

Rejection of Claims 23, 24, 29-33, 36-52 and 99-105 under 35 USC 112 second paragraph:

The Examiner notes that Claims 23, 36 and 99 are confusing in the recitation of "phosphorylation site consensus sequence motif" as it fails to define for what kinase. The Examiner notes that for the purposes of examination the phrase is intended to refer solely to the consensus sequence motif for DNA-PK and further interprets said consensus sequence motif for DNA-PK to be the amino acid pair-enhancer unit of the referenced Claims.

The Applicants respectfully point out that the specification, on page 3, lines 17-23 and page 4, lines 1-12 discuss phosphorylation site consensus sequence motifs. In addition,

on page 4, lines 13-20, the specification states that the goal in designing a good synthetic peptide substrate for a protein kinase is to make one that exhibits "excellent kinetic parameters and a high degree of specificity". These discussions and statements are also present in the grandparent application (see page 2 of U.S. Patent Application Serial No. 08/132,284 filed on October 6, 1993). Thus, the phrase "phosphorylation site consensus sequence motif" is intended to be interpreted in a generic sense – i.e., to encompass any protein kinase phosphorylation site consensus sequence motif. Skilled artisans, at the time of the originally filed application, fully recognized that there were (and still are) any number of protein kinases for which a consensus sequence has yet to be determined. Therefore to prepare a specific synthetic substrate for DNA-PK, a serine/threonine kinase, one of skill in the art would automatically exclude additional serines and threonines from the spacers. By extension this would of necessity also exclude the phosphate-accepting amino acid pairs SQ, TQ, QS or QT from being present in the spacers.

This is also pointed out in the present application (page 75, lines 12-19) and in the grandfather 08/132,284 application of 1993, page 42, lines 7 through 14 which highlights this state of the art in particular for the DNA-PK substrates: "Next, keeping Glu^{11}-Lys^{24}-Lys as the base sequence, individual residues were changed. First, Thr^{18} and Ser^{20} were changed to alanine, **leaving Ser^{15} as the only phosphorylation site (peptide 15, Table 1)**. These changes produced only a twofold increase in K_m and no significant change in V_{max}. Thus, peptide 15, **which has only one possible site of phosphorylation corresponding to that for DNA-PK**, is as good a substrate as was peptide 12 corresponding to the wild-type human p53 sequence, which has another serine and a threonine residue which **may be phosphorylated by other protein kinases**.

Furthermore, in order to ensure that the substrate is specific for only DNA-PK, to one of skill in the art the phrase additionally means the exclusion of other amino acids that are commonly phosphorylated, *i.e.*, tyrosine.

Because Claims 23, 36 and 99, as originally submitted and as amended, cite peptide substrates having a phosphate-accepting amino acid pair and an amino acid pair-enhancer unit, common usage implies that only one amino acid pair and one amino acid pair-enhancer unit would be present in the DNA-PK substrate.

To particularly point out and distinctly claim the present invention, the Applicants have amended Claims 23, 36 and 99 to clearly identify that the generic peptide of the present invention has one phosphate-accepting amino acid pair and that the spacer sequences exclude another phosphorylation site consensus sequence motif.

Because Claims 23, 36 and 99, as originally submitted and as amended, cite a/one phosphate-accepting amino acid pair and an amino acid pair-enhancer unit, and because of the amendment of the Claims herein, the Applicants have cancelled Claims 30, 32, 34, 41, and 43 as the Claims include synthetic peptide substrates that include either more than one amino acid pair or more than one amino acid pair-enhancer unit of the present invention.

Claims 31 and 42 have also been cancelled.

Claims 33, 35 and 44 have been amended as a result of the cancellation of the Claims from which they depend.

Claim 45 has been cancelled and Claims 46 and 47 have been amended as a result of that cancellation.

Claim 102 has been amended to more particularly point out and distinctly claim the negative control peptide of the present invention.

Claim 48 has been cancelled.

Rejection of Claims 24 and 29 under 102(b) as unsupported by the grandparent application:

With respect to Claim 24, please note that Claim 24 has been cancelled herein above.

With respect to Claim 29, the Applicants respectfully request the reconsideration of this basis for its rejection. The argument above, pages 14-16, points to the support found in the present and the grandfather applications that to generate a specific substrate for DNA-PK, a serine/threonine kinase, one of skill in the art would have known to exclude serine and threonine from the spacers and would have also known to exclude tyrosine from the spacers as being an amino acid that is commonly phosphorylated and which would therefore be a potential site for phosphorylation by another kinase.

Rejection of Claims 23 and 30-35 under 35 USC 102 (a or b) as anticipated by Lees-Miller et al. (1992):

The present application is a continuation-in-part of application Serial No. 08/398,139 filed on March 3, 1995, which was a continuation-in-part of U.S. Patent Application Serial No. 08/132,284 filed on October 6, 1993. Thus the present application has a priority date of October 6, 1993 for all common subject matter. This priority date is less than one year after the publication date of November, 1992 in the cited reference. The subject matter disclosed in the Lees-Miller et al. publication is disclosed and/or claimed in the priority application – see specifically page 27, lines 7-14 and Claim 23 of U.S. patent application Serial No 08/132,284.

The Applicant has attached hereto a Declaration under *In re Katz*. In the Declaration it is established that the subject matter published in the cited publication by Lees-Miller et al. is part of the invention described and claimed in the present application. Accordingly, the Lees-Miller et al. publication cannot be prior art against the present application, and it is respectfully requested that this basis for rejection be withdrawn.

Rejection of Claims 23 and 31 under 35 USC 102(b) as being anticipated by Vojtesek et al.:

As noted above, the present application has a priority date of October 6, 1993 for all common subject matter, which common subject matter of the present application as herein amended is based upon the publication of Lees-Miller et al. as noted above. On the face page of the Lees-Miller et al. publication it should be noted that the manuscript was originally submitted for consideration for publication on April 9, 1992 and therefore the basis for the peptide features recited in Claim 23 and 31 were in the inventor's possession prior to the Vojtesek publication.

In addition, the peptides of Claims 23 and 31, as herein amended, are not anticipated by the peptides disclosed in the Vojtesek publication. The peptide residues, 1-37 and 1-53 of p53 all include multiple phosphate-accepting amino acid pairs and additional serine or threonine residues which could potentially represent consensus sequence motifs for another protein kinase.

Thus, the Applicants respectfully request reconsideration and withdrawal of this basis of rejection of Claims 23 and 31.

Rejection of Claims 23, 24 and 31 under 35 USC 102(b) as being anticipated by Lam et al.:

As noted above, the present application has a priority date of October 6, 1993 for all common subject matter, which common subject matter of the present application as herein amended is based upon the publication of Lees-Miller et al. as noted above. On the face page of the Lees-Miller et al. publication it should be noted that the manuscript was originally submitted for consideration for publication on April 9, 1992 and therefore the basis for the features recited in Claims 23 and 31, as herein amended, were in the inventor's possession prior to the Lam publication date of April 15, 1992.

In addition, the peptides of Claims 23 and 31, as herein amended, are not anticipated by the peptides disclosed by Lam et al. as the peptide Pro-17-Gly includes an additional Serine and Threonine which could potentially be phosphorylated by another protein kinase.

Therefore the Applicants respectfully request reconsideration and withdrawal of this basis for the rejection of Claims 23 and 31, Claim 24 having been cancelled by the above amendment.

Joint Inventorship:

The subject matter of the all claims in the present patent application were commonly owned at the time the inventions covered therein were made.

However, with respect to the claims remaining under consideration as a result of the restriction requirement and election, Applicant submits herewith an Amendment, petition and fee deleting a correctly named person who is not the inventor of the invention now being claimed. As a result of the election of the claims remaining in this case, the only inventor of the claims is Dr. Carl W. Anderson.

Rejection of Claims 23, 24, 36-40, 45, 46, 48, 50-52, 99-100 and 102-105 under 35 USC 103(a) as being unpatentable over Chen et al. in view of Glass et al.:

The Applicants respectfully request reconsideration and withdrawal of this basis of rejection in view of the amendment of the claims as herein requested. The TAg peptide discussed briefly in the Chen et al. article, residues 661-674 (TGIDSQSQGSFQAP) has more than one phosphate-accepting amino acid pair and further contains a serine residue (a potential consensus sequence motif for another protein kinase) in the carboxyl-terminal "spacer". Indeed, the diagram in Fig. 9 of Chen et al. shows that Ser-670 (-GS^{670}FQ-) is found to be phosphorylated, and further indicates that it is not phosphorylated by DNA-PK. This suggests that the peptide, Thr-661-Pro-674 does not provide a specific substrate for DNA-PK.

Lees-Miller, et al., in Molecular and Cellular Biology **12**:5041-5049 (1992) provide the first demonstration that it is possible to use DNA-PK to phosphorylate a synthetic peptide substrate having a single phosphate-accepting amino acid pair and a single amino acid pair-enhancer unit using DNA-PK and lacking any other potential phosphorylation consensus sequence motifs. Until that time all phosphorylation reactions of DNA-PK were carried out by labeling intact proteins and peptides having more than one amino acid pair, and/or having additional potential phosphorylation sites. Until the teachings of Lees-Miller et al., there was no evidence that isolated synthetic peptides, having the characteristics of the peptides of the present invention, would have the proper conformation to be phosphorylated efficiently by DNA-PK in vitro.

Therefore, combining the teachings of Chen et al. with the teachings of Glass et al. would not yield peptides of the present invention.

Rejection of Claims 36-52 and 99-105 under 35 USC 103(a) as being unpatentable over Lees-Miller et al. (1992):

As stated above, a Declaration establishing that the subject matter published in the cited publication is part of the invention described and claimed in the present application, which draws its priority date from the filing of the grandparent application (*i.e.*, U.S. Patent Application Serial No. 08/132,284 filed on October 6, 1993) is attached to this paper. Thus, the Lees-Miller et al. publication cannot be prior art against the present application, and the withdrawal of this basis for rejection of the cited Claims is respectfully requested.

Additional Remarks

Rejection of Claim 29 as being unsupported by the grandparent application US Serial No. 08/132,284 filed on October 6, 1993:

On page 5 of the Office Action, the Examiner states:

> "The grandparent application fails to support the specific limitation of . . . . the first and second spacer sequences excluding serine, threonine and tyrosine (Claim 29)."

On pages 8-9 of the Office Action, the Examiner also states:

> "The skilled artisan would have used a peptide highly similar to that of the 661-674 peptide but lacking an essential feature necessary for phosphorylation by DNA-PK. As Chen et al. teach the importance of the SQ sequence for phosphorylation, it would have been obvious to one of ordinary skill to replace one or both of these residues with a similar amino acid (for example alanine for serine or glutamate for glutamine) which would eliminate the SQ phosphorylation site." (emphasis added)

The Applicants submit, for the Examiner's consideration, that the rejection of Claim 29 for lack of support in the grandparent application upon which priority is based is inconsistent with the statement that replacing serine with alanine would be obvious to the skilled artisan. The Applicants therefore respectfully request that the Examiner reconsider the lack of grandparental support basis upon which Claim 29 was rejected since if destruction of the phosphorylation site by its replacement with alanine would have been obvious, the Applicants submit that to design a DNA-PK-specific substrate one would eliminate any amino acids that are commonly phosphorylated from the synthetic peptide substrate and therefore the grandparent patent application does support the exclusion of serine, threonine and tyrosine.

Summary

Cancellation of Claims:

Via this Amendment, Claims 24, 30-32, 34, 41-43, 45, and 48 of the elected invention have been cancelled.

Claims Remaining in the Application:

Amended Claims:

Via this Amendment, Claims 23, 33, 35, 36, 38, 44, 46, 49, 99, 101 and 102 have been amended. The amendments of the Claims contain no new matter.

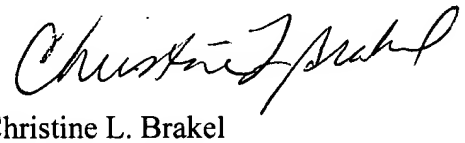
Original Claims:

Claims 29, 37, 39-40, 47, 50-52, 100 and 103-105 are in the listing of Claims in their originally filed form.

References not found in the parent application(s): The Examiner noted that four (4) references could not be found in the applications from which this application draws priority. In accordance with Applicant's duty to disclose, copies of the four (4) references are enclosed with this paper.

In light of the above Amendments and Remarks, applicants respectfully submit that the instant application is now in condition for allowance and solicit a timely notice of allowance.

Respectfully submitted,



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